



**DATE:** January 28, 2010  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *at for LAB*  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# **1607186**  
**TO:** Investigators Using CCI-779 (temsirolimus, Torisel®) (NSC 683864)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent temsirolimus.

The following must be completed by all investigators using temsirolimus under NCI IND 61010:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 61010, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with temsirolimus, there does not appear to be a change in the risk-benefit ratio for temsirolimus, therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 47-year-old female with endometrioid endometrial adenocarcinoma developed a grade 3 periumbilical lesion with ulceration while on a phase 2 trial utilizing the investigational agent temsirolimus.

**ADVERSE EVENTS ASSESSMENT**

IND <b>61010</b> NSC <b>683864</b> CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 3: Ulceration</b>
AE: <b>1607186</b>	Protocol: <b>GOG-0248</b>

The patient is a 47-year-old female with endometrioid endometrial adenocarcinoma who developed a periumbilical lesion with ulceration while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of the investigational therapy on March 26, 2009, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. She received her last dose of temsirolimus on November 5, 2009 (Cycle 6, Day 15).

The patient was initially diagnosed with endometrioid endometrial adenocarcinoma in July 2006, and is status post panniculectomy with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, para-aortic lymphadenectomy, and multiple-agent systemic chemotherapy. She began the investigational therapy on March 26, 2009.

On November 18, 2009 (Cycle 6, Day 28), the patient presented to the emergency room, complaining of excruciating pain under her pannus and in her mons pubis with ambulation. She reported treating herself for a yeast infection with clotrimazole and nystatin powder, which did not alleviate her symptoms. The pain was uncontrolled with oral Dilaudid®. She denied fever, chills, nausea, or vomiting. Physical examination revealed a 6 cm periumbilical lesion with an excoriated, ulcerated base, oozing a purulent discharge. There was also a markedly excoriated, diffuse, rash-type, weeping lesion under the patient's pannus extending onto her thighs and mons pubis. The patient was admitted to the hospital for complicated cellulitis and was started on IV vancomycin, Diflucan®, Dilaudid®, sliding scale insulin, and Glucovance®. On November 19, 2009, a CT scan of the abdomen with and without contrast did not reveal fascial involvement. Wound cultures were positive for a heavy growth of MRSA and moderate growth of *Corynebacterium* species. The pain was controlled with oxycodone. Dry dressings with Kerlix™ were applied to the ulcer. On November 25, 2009, the patient was discharged home on IV antibiotics and wound dressings twice a day managed by Home Health.

The patient's past medical/surgical history is significant for poorly controlled diabetes mellitus and morbid obesity. Medications taken at the time of the event included lisinopril, Celexa®, metformin, Dilaudid®, and Ativan®.

There have been 7 other cases of ulceration reported as serious adverse events through ADEERS under the temsirolimus NSC and/or IND as shown in the table below.

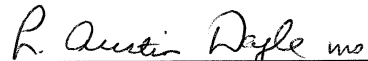
Adverse Event	Grade	Attribution
Ulceration (n=7)	3	1 Unlikely, 1 Unrelated
	2	4 Possible, 1 Unlikely

To date, a total of 1,873 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a possible relationship exists between the event and the investigational agent.

	<b>Ulceration</b>
<b>CCI-779 (temsirolimus, Torisel®)</b>	Possible
<b>Endometrioid endometrial adenocarcinoma</b>	Unlikely
<b>Diabetes</b>	Possible
<b>Obesity</b>	Possible

Date: 1/28/10

Signature:   
L. Austin Doyle, M.D.  
(IDB Monitor for CCI-779)

If this assessment is changed, we will notify your office.

cc: Rafael E. Curiel, Ph.D.  
Wyeth GSSE Triage, [WASDTRI@wyeth.com](mailto:WASDTRI@wyeth.com)  
Wyeth Pharmaceuticals, Inc.